CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

ETHYL BUTYLACETYLAMINOPROPIONATE
BUTYLACETYLAMINOPROPIONIC ACID

Chemical Code # 5359, 5379; Tolerance # 52452

March 4, 1999

I. DATA GAP STATUS

Chronic toxicity, rat:	No study on file; not required at this time[1]
Chronic toxicity, dog:	No study on file; not required at this time[1]
Oncogenicity, rat:	No study on file; not required at this time[1]
Oncogenicity, mouse:	No study on file; not required at this time[1]
Reproduction, rat:	No data gap; No adverse effect
Teratology, Himalayan rabbit:	No data gap; Possible adverse effect
Teratology, NZW rabbit:	No data gap; No adverse effect
Gene mutation:	No data gap; No adverse effect
Chromosome effects:	No data gap; Possible adverse effect
DNA damage:	No data gap; No adverse effect
Neurotoxicity:	Not required at this time

Toxicology one-liners are attached.

All record numbers through 163300 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
indicates a study on file but not yet reviewed.
File name: T172978
Leung, 3/4/99

[1] Toxicology data for ethyl butylacetylaminopropionate and butylacetylaminopropionic acid have been submitted and reviewed as a biochemical pesticide. Toxicity data requirements are set forth under a tiered system. These studies are not required at this time.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

No study on file.

CHRONIC TOXICITY, RAT

No study on file.

CHRONIC TOXICITY, DOG

No study on file.

ONCOGENICITY, RAT

No study on file.

ONCOGENICITY, MOUSE

No study on file.

REPRODUCTION, RAT

** 012; 163289; "Insect Repellent 3535 (Article Number 111887) - 2-Generation Study with Oral Administration to Rats"; (J. Gleich; Institute of Toxicology, Merck KgaA, 64271 Darmstadt, Federal Republic of Germany; Study No. T 9381; 2/7/97); Twenty five Wistar rats/sex/group were treated orally by gavage with 0, 0.1, 0.3, or 1.0 ml/kg/day (equivalent to 99.9, 299.7, or 999 mg/kg /day, respectively) of Insect Repellent 3535 Technical (purity: 98.9%) for two generations. The F0 parents were treated for 10 weeks prior to mating. Mating was completed over a two week interval, followed by 3 weeks of gestation and 3 weeks of lactation. The treatment of 25 weanlings per sex per group (F1 generation) was initiated on post-natal day 28 and continued for 9 weeks. The mating was accomplished over a two week interval, followed by 3 weeks of gestation and 3 weeks of lactation. In the 1.0 ml/kg/day treatment group, one male and one female from the F0 generation and two males and one female from the F1 generation died as a result of treatment. Clinical signs of resistance to dosing, rooting in the sawdust after dosing, and excessive grooming were attributed to aversion to the treatment. Mean liver and kidney weights for mid and high dose F0 males were significantly greater than those of the control males ($p<0.05$). No accompanying histopathological lesions were noted. There were no treatment-related effects on sperm parameters, estrous cycle, mating or fertility. Likewise, there were no effects on the number of implantations or litter size. There was an increase in the number of stillborn pups and pup deaths in the F1 generation at the mid and high dose levels. This was mainly due to the total litter loss of 2 dams in the mid dose group and 3 dams in the high dose group. However, this effect was not repeated in the F2 generation and was not considered to be treatment-related. The growth and development of the pups were not affected by the treatment. **No adverse effect indicated**; **Parental NOEL:** 0.3 ml/kg/day (based upon mortality in the 1.0 ml/kg/day treatment groups); **Reproductive NOEL:** 1.0 ml/kg/day (HTD); **Developmental NOEL:** 1.0 ml/kg/day (HTD); **Study acceptable**. (Moore, 11/13/98)

TERATOLOGY, RAT

No study on file.

TERATOLOGY, HIMALAYAN RABBIT

**** 011; 163288**; "Insect Repellent 3535 (Article Number 111887) - Developmental Toxicity Study with Oral Administration to Rabbits"; (J. Gleich; Institute of Toxicology, Merck KGaA, 64271 Darmstadt, Federal Republic of Germany; Study No. T 9382; 7/22/96); Fifteen mated female Himalayan rabbits/group were treated orally by gavage with 0, 0.1, 0.3 or 1.0 ml/kg/day (equivalent to 0, 99.9, 299.7 or 999 mg/kg/day, respectively) of Insect Repellent 3535 Technical (Article Number 111887) (purity: 98.9%) from gestation day 6 to 19. One female in the 0.3 ml/kg group died on day 26. Six females in the 1.0 ml/kg group died or were euthanized *in extremis*. Five of these deaths occurred during the treatment period. The animals in the high dose group suffered significant weight loss and reduced food consumption between gestation days 6 and 13. The does in the 0.3 ml/kg group demonstrated reduced food consumption during the first week of dosing. Pathological examination of the decedent animals revealed that three of the does in the 1.0 ml/kg group demonstrated multifocal erosion of the stomach. Two of the animals in this group also suffered from tubular degeneration and edema in the Bowman's capsule of the kidneys. In fetal development, there was a significant increase in the number of litters with early resorptions at the 0.3 ml/kg treatment level (control: 2/14, 0.1: 6/15, 0.3: 8/14, 1.0: 4/7). The number of fetuses with malformations in the 0.1 ml/kg group was greater than the control value (0/63 vs. 6/80). These malformations included open eye (unilateral) (1 fetus), anasarca (1 fetus), flexed limbs (3 fetuses), and fused sternabrae (1 fetus). In addition, one of the fetuses suffered from multiple malformations. None of these effects targeted a particular organ. Otherwise, no other effects were noted on fetal development. **Possible adverse effect:** increased incidence of early resorptions. **Maternal NOEL:** 0.1 ml/kg/day (based upon mortality and treatment-related effect upon food consumption in the 0.3 ml/kg group); **Developmental NOEL:** 0.1 ml/kg/day (based upon the increased incidence in early resorptions in the 0.3 ml/kg group). **Study acceptable.** (Moore, 12/15/98)

52452-011; 163288; "Insect Repellent 3535 (Article Number 111887) - Addendum to Developmental Toxicity Study with Oral Adminstration to Rabbits"; (J. Gleich, *et.al.*; Institute of Toxicology, Merck KGaA, 64271 Darmstadt, Federal Republic of Germany; Study No. T 9382; 3/4/97); Insect Repellent 3535 Technical (Article Number 111887) (purity: 98.9%) was administered orally by gavage at a dose of 0 or 1.0 ml/kg/day (equivalent to 999 mg/kg/day) to female Himalayan rabbits. In the control group, five non pregnant animals were dosed for 18 days. In group 2, five non pregnant rabbits were dosed for 4 to 9 days with the test material. In the third group, five pregnant animals were dosed with the test material for 5 to 11 days, starting on gestation day 6. Two of the group 2 rabbits died on days 7 and 8 of treatment. The other three animal were euthanized *in extremis* on days 4, 6 and 8. In group 3, one female died after 5 days of treatment. The other four animals were euthanized *in extremis* on days 4, 5 (2 animals) and 10. Animals which were euthanized had not eaten or drunk water for several days. Body temperature was reduced for both groups of treated animals from the first day of treatment with the effect being more pronounced as the treatment progressed. Blood pressure was lower for the 2 treated animals each examined in both groups than for the 2 control animals (determined after 8 days of treatment). Various serum chemistry parameters were affected by the treatment. However, the blood samples were collected when the animals were quite sick and the effects may have been secondary to the general health of the animal. Histopathological evaluation of the treated animals revealed hemorrhages and erosions in the gastric mucosa and intestinal tract, vacuolar degeneration of parenchymal cells and hemosiderosis in the liver, deposition of protein in the Bowman's space of the kidney. Atrophy of the bone marrow was also noted for one rabbit. **Supplemental Study**. (Moore, 1/25/99)

52452-011; 163288; "Insect Repellent 3535 (Article Number 111887) - Investigatory Study T 9385 with Oral Administration to Rabbits"; (J. Gleich, *et. al.*; Institute of Toxicology, Merck KGaA, 64271 Darmstadt, Federal Republic of Germany; Study No. T 9385; 3/11/97); Five non pregnant female Himalayan rabbits/group were dosed orally by gavage with 0.1 or 0.3 ml/kg/day (equivalent to 100 or 300 mg/kg/day, respectively) of Insect Repellent 3535 Technical (Article Number 111887) (purity: 98.9%) for 10 days. No mortality resulted from the treatment. Both groups demonstrated a slight mean body weight loss over the course of the treatment. Body temperatures were not affected by the treatment. No significant alterations were noted for the hematological or serum chemical parameters. In the gross examination, foci of red or black discoloration of the mucous membrane in the stomach/cecum was noted for one rabbit in the low dose and 3 rabbits in the high dose groups. Histological evaluation revealed hemorrhages in the gastric mucosa of 2 animals each in both groups. In addition, one animal in the high dose group exhibited small focal necroses in the gastric mucosa, another had hemorrhages in the muscularis and submucosa with accompanying local inflammation, and a third animal demonstrated localized edema in the gastric mucosa. Atrophy of cells in the mucous membrane was noted for one and two animals in the low dose and high dose groups, respectively. **No adverse effect indicated. Study supplemental.** (Moore, 12/15/98)

52452-011; 163288; "Insect Repellent 3535 (Article Number 111887) - Investigatory Study T 9400 with Oral Administration to Himalayan and New Zealand White Rabbits"; (J. Gleich, *et. al.*; Institute of Toxicology, Merck KGaA, 64271 Darmstadt, Federal Republic of Germany; Study No. T 9400; 3/11/97); Three female Himalayan and New Zealand White rabbits were dosed orally by gavage with 0.6 ml/kg/day (equivalent to 600 mg/kg/day) of Insect Repellent 3535 Technical (Article Number 111887) (purity: 98.9%) daily for 10 days. Plasma levels of the test material were determined at 0.5, 1, 3, 6 and 24 hours after dosing on the first and 10th days of dosing. No mortality resulted from the treatment. After an initial loss in weight, all of the animals gained weight over the course of the treatment. Peak plasma concentrations of the test material were achieved 30 minutes to 1 hour after dosing. No accumulation in the plasma was evident after repeated dosing. Localized hemorrhages were noted in the gastric mucosa of one of the Himalayan rabbits in the gross examination. Histopathological evaluation revealed atrophy of the mucous membrane in the gastric fundus of two Himalayan rabbits and one New Zealand rabbit. **No adverse effect indicated. Study supplemental**. (Moore, 12/15/98)

TERATOLOGY, NZW RABBIT

** 010; 163287; "A Developmental Toxicity Study of IR 3535 in Rabbits"; (J.L. Schardein; WIL Research Laboratories, Inc., Ashland, OH; Study No. WIL-149021; 2/19/97); Twenty artificially inseminated female New Zealand White rabbits/group were treated orally by gavage with 0 (1% aqueous CMC/0.1% Tween 80), 100, 300, or 600 mg/kg/day of IR 3535 Technical (purity: 99%) from day 7 through day 19 of gestation. No mortality resulted from exposure to the test material. No treatment-related effects on the does were evident. Likewise, no treatment-related effects were noted on development of the fetuses. **No adverse effects** indicated. **Maternal NOEL:** 600 mg/kg/day, **Developmental NOEL:** 300 mg/kg/day (based on reduced body weight gain and food consumption on days 7 through 10 of gestation and reduced defecation). Although an apparent maximally tolerated dose was not achieved in the study, the highest dose level was sufficient to evaluate the potential developmental toxicity of the test material. **Study acceptable.** (Moore, 10/23/98)

009; 163285; "A Dose Range-Finding Developmental Toxicity Study of IR 3535 in Rabbits"; (J.L. Schardein; WIL Research Laboratories, Inc., Ashland, OH; Study No. WIL-149020; 3/7/97); Six artificially inseminated female New Zealand White rabbits/group were treated orally by gavage with 0 (1% aqueous CMC/0.1% Tween 80), 50, 100, 300, 600 or 1000 mg/kg of IR 3535 Technical (purity: 99%) from day 7 through 19 of gestation. No mortalities occurred as a result of exposure to the test material. Mean body weight loss was reported between gestation days 7 and 10 for both the 600 and 1000 mg/kg/day groups and between days 10 and 13 in the 1000 mg/kg/day

group. Food consumption was concurrently less for both of these groups. No apparent-treatment related effects on the development of the fetuses. **No adverse effect indicated. Parental NOEL:** 300 mg/kg/day; **Developmental NOEL:** 1000 mg/kg/day; **Study supplemental.** (Moore, 11/16/98)

52452-009; 163286; "A Two-Week Repeated Dose Toxicity Study of IR 3535 in Non-Pregnant Rabbits"; (J.L. Schardein; WIL Research Laboratories, Inc., Ashland, OH; Study No. WIL-149022; 1/6/97); Six female non-pregnant New Zealand White rabbits/group were dosed orally by gavage with 0 (1% aqueous CMC/0.1% Tween 80) or 600 mg/kg/day of IR 3535 (purity: 99%) for 14 days. No mortality resulted from the treatment. Treated group suffered a minimal loss in body weight during the first 5 days of treatment in conjunction with reduced food consumption during this period. There was no treatment-related effect upon body temperature. No treatment-related lesions were noted during gross necropsy at the termination of the study. **No adverse effects indicated. Supplemental study**. (Moore, 12/11/98)

GENE MUTATION

** 013; 163290; "Insect Repellent 3535 (Article Number 111887) - Bacterial Mutagenicity Assay, *Salmonella typhimurium* and *Escherichia coli*"; (D. Utesch; Institute of Toxicology, Merck KGaA, 64271 Darmstadt, Federal Republic of Germany; Project No. T13942; 7/19/96); *S.typhimurium* strains TA 98, TA 100, TA 102, TA 1535, and TA 1537 and *E. coli* WP2 uvrA were treated for 48 hours at 37^{o} C with Insect Repellent 3535 Technical (Article Number 111887) (purity: 98.9%) at concentrations ranging from 5 to 5000 µg/plate (trial #1) or 50 to 5000 µg/plate (trial #2) with and w/o activation. Each treatment level was plated in triplicate (solvent controls: 6 plates). An Aroclor 1254-induced rat liver S9 fraction was used to activate the test material. There was no treatment-related increase in the incidence of reverse mutation. **No adverse effect indicated. Study acceptable.** (Moore, 12/16/98)

** 013; 163294; "Insect Repellent 3535 (Article Number 111887): Mammalian Cell (V79) Gene Mutation Test"; (F. Oesch and J.G. Hengstler; Institute of Toxicology, University of Mainz, 55131 Mainz, Federal Republic of Germany; Report No. AFP 128; 6/26/96); Chinese hamster V79 cells were treated with Insect Repellent 3535 Technical (Article Number 111887) (purity: 99.0%) at concentrations ranging from 0 to 5000 µg/ml for 3 hours (activation) or 24 hours (non activation). Two trials were performed with at least duplicate cultures for each treatment level. An Aroclor 1254-induced rat liver S9 fraction was used to activate the test material. No treatment-related increase in forward mutations in the hprt locus was evident. **No adverse effect indicated. Study acceptable.** (Moore, 12/13/98)

CHROMOSOME EFFECTS

**** 013; 163292**; "Chromosomal Aberrations in Chinese Hamster Ovary (CHO) Cells with and without Exogenous Metabolic Activation"; (H. Murli; Corning Hazleton Inc., Vienna, VA; Study No. 17982-0-437;11/25/96); Chinese hamster ovary (CHO-WBL) cells were exposed to IR 3535 Technical (purity: 98.9%) at concentrations ranging from 0 to 3000 µg/ml (non activated), 0 to 5000 µg/ml (activated, Trial #1) or 0 to 4990 µg/ml (activated, Trial #2). In the non activated samples, the cells were incubated for 27.8 hours with the test material. The cells in the activated samples were incubated for 3 hours with the test material, followed by an additional 25 hour period. In both assays, the cells were incubated in the presence of Colcemid for 2 more hours prior to fixation. All of the incubations were performed at 37^{0} C with duplicate cultures for each treatment level. An Aroclor 1254-induced rat liver S9 fraction was used to activate the test material. A treatment-related increase in the percentage of cells with chromosomal aberrations was noted for the activated samples ($p < 0.01$). **Adverse effect indicated. Study acceptable.** (Moore, 12/22/98)

DNA DAMAGE

** 013; 163293; “Insect Repellent IR 3535 (Art. No. 111887): Induction of Micronuclei in the Bone Marrow of Treated Mice”; (R. Marshall; Corning Hazleton (Europe), North Yorkshire HG3 1PY, England; Report No. 221/12-1052; 9/17/96); Five mice/sex/group/time point were treated intraperitoneally with 0, 475, 950, or 1900 mg/kg of Insect IR 3535 (Art. No. 111887) (purity: 99.0%) and euthanized 24, 48 or 72 hours after dosing. An additional 5 animals/sex were treated with the positive control (cyclophosphamide, 40 mg/kg) and euthanized 24 hours after dosing. Bone marrow samples from the femur were examined and the ratio of polychromatic (PCE) to normochromatic (NCE) and the percentage of PCE with a micronucleus were determined. No treatment-related increase in the number of PCE with a micronucleus was noted. **No adverse effect indicated. Study acceptable.** (Moore, 12/22/98)

NEUROTOXICITY

No study on file.